DETAILED ACTION

Summary

1. The amendment filed on Dec. 14, 2009 has been noted Claims 1, 14, 18, 26 and 33 have been amended. Claims 5, 25, 32, 36 have been canceled. New claims 47-52 have been added. Claims 1-5, 6-8, 14-24, 26-31, 33-35, 41-43 and 47-52 are pending. Claims 1-5, 6-8, 14-24, 26-31, 33-35, 41-43 and 47-52 are examiner.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 1-5, 6-8, 14-24, 26-31, 33-35, 41-43 and 47-52 are still rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

4. In the response, Applicants submit the following arguments to traverse the rejection:

5. 1). The adaptive mutations cited in the claims are relative to the post-translational polypeptide of the H77c depicted at GenBank accession number AF011751 (see Table 2) set forth in SEQ ID NO:2, the skilled person is therefore, able to ascertain where to identify the amino acid positions recited in the claims.

6. 2). HCV is an RNA virus that depend an RNA depended RNA polymerase to replicates virus. This enzyme has a significant lower fidelity of than DNA polymerase. Therefore, there is an expectation that precise position for an adaptive mutation varies in different HCVs as described in the specification pages 14-16. For at least these reasons, the claims are not indefinite.

7. 3). The independent claims 1, 14, 18, 26 and 33 have been amended to cite the percentage identity of the amino acid sequence encoded by the claimed polynucleotide having at least 90% to the amino acid sequence of SEQ ID NO: 2. Therefore, the rejection should be withdrawn.

8. Applicants' amendment and argument have been respectfully considered; however, it is not found persuasive for the reasons set forth below:

9. 1). The limitation of the numeric number based on SEQ ID NO: 2 is not cited in any or the independent claims.

10. 2). In contrary to applicants' assertion, because HCV has a high tendency to be mutated autonomously and it comprises many quasispecies, it is necessary to define the structure of any claimed HCV mutation in any claim, such that the searching and determining the patentability for any claimed HCV mutant can be made accordingly.

11. 3). the citation of the amino acid sequence have at least 90% identity in claims are confusing because 1). it does not define to which the 90% identity is compared, and 2). it does not limit the said HCV polyprotein should have any mutation cited in the claims beside a 90% identity to an amino acid sequence undefined.

12. 4). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

13. To this content, claims 1-5, 6-8, 14-24, 26-31, 33-35, 41-43 and 47-52 are still rejected.

Claim Rejections - 35 USC § 112

14. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

15. Claims 1-5, 6-8, 14-24, 26-31, 33-35, 41-43 and 47-52 are still rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for having an isolated replication competent polynucleotide encoding a HCV polyprotein with particular adaptive substitution mutations at amino acid residue S2204I in combinations with K1694R, F2080V and Q1609R or S2204I in combinations with K1694R and Q1609R relatively to the parental amino acid sequence set forth in SEQ ID NO: 2, wherein such mutations make the HCV replicon being capable of replication competent,

does not reasonably provide enablement for having a polynucleotide being replication competent as long as the HCV polynucleotide sequence encoding a polynucleotide comprising 5' and 3' non-coding region (NCR) and having at least 90% identity to an amino acid sequence undefined but within the HCV genotype 1a. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected to make and use the invention commensurate in scope with these claims.

16. In the response, Applicants traverse the rejection with following arguments:

17. 1). The claims have been amended to limit the claimed polynucleotide encoding the variants of genotype 1a HCV and comprising the 5' NTR and 3' NTR;

18. 2). Prior to the current Application was filed, many nucleotide sequences of genotype 1a HCV were known, the toll for comparing different sequences between different HCV were also available as well as the crystal structures of some HCV proteins were also known. Thus, a skilled person would have known which nucleotides and /or amino acids could be mutated and not affect replication.

19. 3). The specification clearly identifies operative embodiments, and undue experimentation is not required to determine which conceived but not unmade embodiments are operative according to M.P.E.P. 2164.04., the presence of inoperative embodiments within the scope of a claim does not necessarily render a claim not enabled. The standard is whether a skilled person could determined which embodiments that were conceived, but not yet made, would be operative with expenditure of no more effort than is normally required in the art.

20. 4). The examiner fails to establish the basis to question the enablement provided for the claimed invention.

21. Applicants' argument has been respectfully, however, it is not persuasive to overcome the rejection for the reasons cited in the previous office action, which is substantiated with the more detail explanations hereto.

22. In the previous office action, the enablement rejection is made because the broadly claimed scope is not supported by insufficient support and guidance provided by the specification, especially in view of the highly unpredictable field as evidenced by

Applicants' own disclosure and state of art at the time when the current Application was filed. Applicants do not describe which 10% over 3011 amino acids in the HCV genotype 1a can be mutated such that the HCV replicon can be replication competently, especially in view of the highly unpredictable field.

23. For example, the previous office action cites: The state of art teaches that subgenomic HCV can be used for making a replicon to express HCV polyprotein in full or in part. However, the random mutation(s) made intentionally or unintentional is very unpredictable regarding the replication ability of a HCV replicon in host cells as experienced and evidenced by artisans in the field including Applicants themselves (please see Yi et al. J. Virol. 2004, Vol. 78, No. 15, pp. 7904-7915). Yi et al. demonstrate that the combination of the consensus mutation S2204I in combination with mutation F2080V or K1691R or Q1067R alone does not replicate in host cell. Even the consensus mutation S2204I in combinations with Q1067R and F2080V makes the resulting HCV replicon not replication competent (See Fig. 4, especially the Fig. 4C).

24. While Applicants asserted that many HCV sequences and particular viral protein(s) that play a fundamental role for controlling the HCV replication property had been described by the time the current Application was filed, the problem for assuring a HCV replicon being able to replicate competently with a point mutation had not been solve by the time when the Application was filed and it is still unclear which point mutation is important for maintaining or increasing the replication competency for HCV replicon so far.

25. For example, Cheney et al. (Virology 2002, Vol. 287, pp. 298-306), a reference provided by IDS in the response, teach that HCV viral polymerase located in NS5B protein, and especially the β-haripin containing six conserved sequence motifs, play a central role in replication of HCV. A mutation of a single amino acid in this motif results in complete lost the HCV RNA replication property (See Fig. 4). But when replicon RNA carrying the β-haripin truncation was incapable of producing drug-resistance colonies, the NS5B protein with such truncation possess significant higher enzymatic activity than the wild-type protein. On the other hand, no reduction in polymerase activity was observed when the β-haripin in NS5B was shorted by four or eight amino acid

residues, a significant enhancement in both prior-depended and de novo initiation activity was observed. However, when these truncations were introduced into the replicon RNA, it completely lost the ability to replicate in Huh-7 cells. Therefore, Cheney et al. concluded that it is unclear which of the potential functions is crucial for HCV RNA replication in the infected cells. (See pages 302-304).

26. While many nucleotide sequences of HCV genotype 1a had been known prior to the current Application was filed, and Applicants describe that about up to 1 to 10% of HCV genome can be mutated, but it is still unclear where a replication competent mutation should be precisely made. It is worth to note that mutants with 10% of 3011 amino acids in variety combination with19 amino acids alteration(s) would be an astronomic numbers of choices. Without precise guidance, a person skilled in the art would have to do undue experimentation to fulfill the broad scope encompassed by the claims with unpredictable outcomes or success.

27. As discussed above, the rejection is maintained.

Conclusion

No claims are allowed.

1. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to BAO LI whose telephone number is (571)272-0904. The examiner can normally be reached on 6:30 am to 3:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Patrick Nolan can be reached on 571-272-0847. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Bao Qun Li/
Examiner, Art Unit 1648

/Patrick J. Nolan/
Supervisory Patent Examiner, Art Unit 1648

Search Notes (continued)

Application/Control No.	Applicant(s)/Patent under Reexamination	
10/580,979	LEMON ET AL.	
Examiner	**Art Unit**	
BAO LI	1648	

SEARCHED			
Class	Subclass	Date	Examiner

INTERFERENCE SEARCHED			
Class	Subclass	Date	Examiner
Updated SEQ ID NO: 2 and consesus mutations S2204I in PTO		3/7/2010	BLI

SEARCH NOTES (INCLUDING SEARCH STRATEGY)		
	DATE	EXMR
Updated ODP search in EAST and eDAN	3/10/2010	BLI
updated SEQ ID NO: 2 search in PTO and commercial date date including the framgnet comprising S2204I	3/10/2010	BLI
112 1st and 2nd paragraph rejections discussed with P. Nolan	3/7/2010	BLI